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(54) Title: DERMATITIS TREATMENT COMPOSITIONS CONTAINING SULPHUR, SALICYLIC ACID AND DIME-THYLSULPHONE (57) Abstract The present invention relates to synergistic composition comprising sulphur with salicylic acid or a physiologically acceptable salt or ester thereof and methylsulphonylmethane and their use in formulations and methods of treatment and prophylaxis of housewife dermatitis and for protecting and improving skin condition.		

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DERMATITIS TREATMENT COMPOSITIONS CONTAINING SULPHUR, SALICYLIC ACID AND DIMETHYLSULPHONE

Housewife dermatitis is a very common condition which continues to raise considerable interest not only because of the complex mechanisms involved in its development, but also because of the therapeutic challenge it poses. The condition represents the injury inflicted on the skin of the fingers and hands following contact with household detergents, cleansing agents and purifying substances. The dermatitis manifests itself by dryness, roughening, thickening and fissuring of the fingers and hand. Exposure to sunlight for long periods, air pollutants and environmental irritants, promote the dermatitis and enhance its severity.

Housewife dermatitis remains a difficult condition to treat and it is, thus, the aim of the present invention to introduce an effective therapy which not only removes the dermatitis but also protects against its recurrence.

The mechanism responsible for the development of housewife dermatitis is complex. Although an extensive range of products is available on the market, none is designed to combat the factors behind the development of the dermatitis and none opposes the mediators of skin injury and damage which represent the final common pathway through which irritants such as detergents, produce their adverse skin effects. The present invention aims, therefore, at directly addressing these issues by providing a synergistic composition which not only effectively treats housewife dermatitis and enhances its healing, but also protects against the recurrence of this condition. It follows that application of this invention to the skin improves its condition and maintains its texture and vitality.

The invention provides a synergistic composition

suitable for use in the treatment of housewife dermatitis, which composition comprises precipitated sulphur with salicylic acid and methylsulphonylmethane.

In accordance with the present invention, the application of the composition to the skin of the hands has been found in a surprising and very unexpected manner to improve its condition in a number of ways including protection against irritation, maintenance of texture and vitality, and in particular the protection against and treatment of housewife dermatitis. It has also been noted that the composition has the advantageous property of adhesion to the skin thereby affording prolonged contact and enhanced therapeutic delivery. Moreover, the ingredients of the composition interact in a synergistic manner in that the sum of the action of all the ingredients used separately is less than that exhibited by the composition.

Advantageously, there is also included a vasodilator such as menthol in order to further increase the effectiveness of the composition in the skin.

In a further aspect, the present invention provides a composition of the invention in intimate admixture with a physiologically acceptable carrier, for use in improving the condition of the skin of the hands.

In another aspect, the present invention provides a topical formulation comprising a composition of the invention in intimate admixture with a pharmaceutically acceptable vehicle. The vehicle should be 'acceptable' in terms of being generally non-deleterious to the skin of the subject being treated and compatible with the other ingredients of the formulation. It will of course be appreciated that certain individuals have

significantly more sensitive skins than the average and that in these special cases alternative vehicles to those normally used may need to be tried.

Suitable vehicles are well known in the art being noted for example in such standard works as the British Pharmacopoeia and the British National Formulary and include ointment bases and cream bases as well as lotions, pastes, jellies, sprays, aerosols and bath oils. Ointments and creams may contain oleaginous absorption colloidal clays, thickening agents such as gum tragacanth or sodium alginate and other pharmaceutically acceptable accessory ingredients such as humectants, preservatives, buffers and antioxidants which have utility in such formulations.

Cream formulations are usually preferred as being most acceptable to the majority of users. A particularly convenient base is one utilizing cetomacrogol, comprising for example 30% w/v cetomacrogol emulsifying ointment (30% w/v cetomacrogol emulsifying wax, 20% w/v liquid paraffin wax, 50% w/v white soft paraffin) in freshly boiled and cooled purified water with for example 0.1% w/v chlorocresol or 0.08% w/v propyl hydroxybenzoate, 0.15% w/v methyl hydroxybenzoate and, 1.5% w/v benzyl alcohol.

In general, the compositions of the present invention contain at least 0.5% w/w of each of the active ingredients preferably from 1 to 20% w/w, and most preferably from 2 to 10% w/w. These dosage levels do not, however, indicate that the relative ratios of the active ingredients should be identical.

Advantageously, the compositions of the invention may be administered in a slow release or sustained release

topical vehicle so that a prolonged therapeutic effect may be achieved.

The frequency of the topical application depends on the indication. When dermatitis is being treated, a liberal amount of the cream is gently rubbed for a few minutes into the skin of the hands 2 or 3 times a day. It is advisable to leave the evening application overnight to enhance the repair of the skin damage and to stimulate healing. For prophylaxis against housewife dermatitis, or for the maintenance of the vitality of the hands' skin and for the prevention of its dryness or roughening and fissuring, a once daily application, as stated above, suffices. Each application must be washed away with warm water before another one is used. Contact with the eyes and oral consumption must be avoided.

While not restricting the scope of the present invention, it is believed that the mechanism of action behind its beneficial effects involves to some degree scavenging the cytotoxic oxygen-derived free radicals which mediate tissue injury.

Further preferred features and advantages of the invention will be realised from the following Examples, which are presented by way of illustration only.

Example 1 - Preparation of cream for skin treatment

A. methylsulphonylmethane	5g
precipitated sulphur	4g
salicylic acid	2g
cetomacrogol 'A'	add to 100g

B. methylsulphonylmethane	5g
precipitated sulphur	4g
salicylic acid	2g
menthol crystals	1g
cetomacrogol 'A'	add to 100g

These compositions should be prepared at a temperature of 25°C. The powder form of the active ingredients is mixed well in a glass or stainless steel container and then the appropriate amount of cetomacrogol 'A' is added and mixed for 10 minutes. When menthol is being used, this should first be finely ground. The composition is allowed to stand for one hour then placed in dark-coloured non-transparent glass containers and stored at temperatures not exceeding 26°C. After preparation the formulation should not be used for at least 12 hours and should not be left for too long exposed to the air or direct sunlight.

Example 2 - Use of topical cream

The formulations illustrated in Example 1 may be used 1 to 3 times daily depending on whether the application is being administered for prophylactic or therapeutic reasons. To protect the skin of the hands and fingers against the damage incurred by detergents and household agents, and to maintain its texture and prevent drying up, a once daily application is generally recommended. A liberal amount of the cream is spread over the skin of the hands or the area to be treated, and gently rubbed in for a few minutes. For therapeutic purposes, a second application is indicated and preferably used in the evening and left overnight. A fresh application should not be used without having washed away the previous one, and this may be done using warm water alone.

Treatment may be for a few days or weeks depending on each case and in particular the individual's existing skin condition and requirements.

Example 3 - Detailed evaluation of the compositions and their active ingredients

Consecutive females who had been diagnosed to have housewife dermatitis (roughening, thickening and fissuring of the skin of the fingers and hands), were prospectively randomized (by drawing sealed envelopes) on a double blind basis, to treatment with various agents presented in a cetomacrogol 'A' base or with this base alone (control group), to study the therapeutic effect of their twice daily application for four weeks, as shown in the Table below. Ten females were allocated to each group and the overall age range for the study was 31 to 55 years. A successful therapeutic outcome was judged objectively by observing a complete healing of all the fissuring coupled with a return of the skin texture to its original smoothness.

Table : Effect of housewife dermatitis treatment

Treatment group (n = 10)	successful therapy
cetomacrogol 'A'	0
sulphur 1%	0
sulphur 2%	0
sulphur 5%	0
sulphur 10%	0
salicylic acid 1%	0
salicylic acid 2%	0
salicylic acid 5%	0
salicylic acid 10%	0
sulphur 1% + salicylic acid 1%	10%
sulphur 2% + salicylic acid 2%	20%
sulphur 5% + salicylic acid 5%	30%
sulphur 10% + salicylic acid 10%	30%
MSM 1%	10%
MSM 2%	10%
MSM 5%	30%
MSM 10%	30%
MSM 1% + sulphur 1% + salicylic acid 1%	40%
MSM 2% + sulphur 2% + salicylic acid 2%	80%
MSM 5% + sulphur 5% + salicylic acid 5%	100%
MSM 10% + sulphur 10% + salicylic acid 10%	100%

MSM : methylsulphonylmethane

The results of this study clearly demonstrate that while neither sulphur nor salicylic acid exert any beneficial therapeutic effects against housewife dermatitis, their combination together affords some therapeutic gains. The addition, however, of methylsulphonylmethane synergistically intensifies these gains. Moreover, the results support the choice of the doses employed in Example 1 as being optimal.

Example 4 - Clinical trials

These trials were carried out in females on a prospective randomized (by drawing sealed envelopes) double blind basis to examine the effect of a particular treatment in comparison with that of its base (cetomacrogol 'A') alone (control group). The treatment code was only broken at the end of the trial period.

A. The therapeutic effect of the formulation described under Example 1.B against housewife dermatitis when applied twice daily for 6 weeks was examined. Housewife dermatitis refers to thickening, roughening and fissuring of the skin of the fingers alone or with that of the main part of the hand. Twenty-six females (age range 32 to 55 years - mean 43) randomized to the control group and 24 females (age range 35 to 51 years - mean 42) randomized to the treatment group were fully evaluable. While no beneficial therapeutic effect occurred in the control group, this was realized in all the active therapy group cases (100%). These women were observed to have acquired complete healing of their skin's fissures and a return of the skin's smoothness and originally normal texture and appearance.

No adverse effects or allergies were noticed in any case.

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B. The efficacy of the formulation described under Example 1.A in allaying symptomatic relief, was examined in women who complained of itching and hyperaesthesia upon contact with detergents and other household chemicals but who had no obvious signs of dermatitis. The formulation or its base were applied onto the hands twice daily for ten days during the period of exposure. Twenty controls (age range 32 to 51 years - mean 40) and 21 treatment cases (age range 31 to 49 years - mean 38) were fully evaluable. Complete symptomatic relief was attained by all the active therapy cases (100%), but in none of the controls. No adverse effects, allergies or hypersensitivities were incurred by the active treatment.

C. The prophylactic effect of the formulation described under Example 1.B against the recurrence of housewife dermatitis, after it had been successfully treated, was investigated. All women were instructed to continue their routine housework as they did before they sought treatment for their dermatitis, and were instructed to apply their regimen as a hand cream, but leaving it overnight and washing it away in the morning with warm water. Treatment lasted for four months (end point of the study). Twenty-five females (age range 28 to 54 years - mean 39) in the control group and 23 females (age range 31 to 51 years - mean 36) in the active therapy group were fully evaluable. Complete protection against the recurrence of housewife dermatitis with maintenance of the hands' smoothness and normal skin texture was observed in all members of the active therapy group (100%), but in none of the controls.

Prolonged administration incurred no local or systemic adverse effects and was very well tolerated by all the cases studied.

Example 5 - Toxicity studies

Groups of ten healthy male volunteers of an age range between 18 and 40 years were studied. The following formulations were prepared in a cetomacrogol 'A' base as generally detailed in Example 1:

1. methylsulphonylmethane 1% +
sulphur 1% + salicylic acid 1%
2. methylsulphonylmethane 2% +
sulphur 2% + salicylic acid 2%
3. methylsulphonylmethane 5% +
sulphur 5% + salicylic acid 5%
4. methylsulphonylmethane 10% +
sulphur 10% + salicylic acid 10%
5. methylsulphonylmethane 15% +
sulphur 15% + salicylic acid 15%

The formulations were applied twice daily for ten days onto the shoulders and arms. Each application consisted of a liberal amount of the cream spread over the shoulders and arms then gently rubbed in for a few minutes. Three hours later, the application was washed away with warm water. Physical examination was carried out once every day during the ten days of study. Similarly, standard haematology and biochemistry tests (including liver and urinary function tests, blood glucose, serum amylase and blood gases) with urine examination were performed every day. An electrocardiogram with cardiac enzymes' level estimation were taken every other day.

All the therapeutic doses were comfortably tolerated without any apparent allergic or adverse reactions. In addition, no toxicity was produced by any of these doses. It is, consequently, concluded that the formulations described under Example 1 are safe for clinical use in the recommended doses.

It will be appreciated that although the sulphur with salicylic acid and methylsulphonylmethane components are generally used in similar amounts, by weight, in the synergistic compositions of the invention, other ratios may also be used. Generally there is used a ratio of from 30:1 to 1:10, preferably from 15:1, most preferably from 3:1 to 1:1, by weight.

Furthermore the relative proportions of sulphur and salicylic acid may also be varied e.g. between 10:1 and 1:5, preferably 5:1 to 1:1, advantageously approximately 2:1.

For the avoidance of doubt it should be noted that the terminology "housewife dermatitis" is not in any way intended to indicate a gender-specific condition or that use of the compositions and treatments of the invention is restricted to the female gender.

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CLAIMS

1. A synergistic composition, which composition comprises sulphur with salicylic acid or a physiologically acceptable salt or ester thereof and methylsulphonylmethane.
2. A composition according to claim 1 wherein said sulphur with salicylic acid or a physiologically acceptable salt or ester thereof and methylsulphonylmethane are present in a ratio of from 15:1 to 1:5 by weight.
3. A composition according to claim 1 or claim 2 wherein said sulphur and salicylic acid are present in a ratio of from 10:1 to 1:5.
4. A composition according to any one of claims 1 to 3 wherein said sulphur is in the form of precipitated sulphur.
5. A composition comprising sulphur with salicylic acid or a physiologically acceptable salt or ester thereof and methylsulphonylmethane for use in the preparation of a formulation for the treatment and prophylaxis of housewife dermatitis.
6. A formulation comprising a composition according to any one of claims 1 to 4 in intimate admixture with a physiologically acceptable carrier therefor, for use in improving the condition of the skin.
7. A topical formulation according to claim 6 which contains at least 0.5% w/w of each of the sulphur with salicylic acid or a physiologically acceptable salt or ester thereof and the methylsulphonylmethane.

8. A formulation according to claim 7 which contains from 1 to 20% w/w of each of the sulphur with salicylic acid or a physiologically acceptable salt or ester thereof and the methylsulphonylmethane.

9. A method of prophylaxis or treatment of housewife dermatitis which comprises administering an effective dosage of a formulation according to claim 6.

10. A method of protecting and improving skin condition which comprises administering an effective dosage of a formulation according to claim 6.

11. A method according to claim 9 or claim 10 wherein is applied to the skin a topical formulation according to claim 7.

12. A method according to claim 11 wherein said topical formulation is applied to the skin at least 2 times per day.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/GB 93/01873

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K33/04 //(A61K33/04,31:60,31:10)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB,A,2 057 263 (HERSCHLER R. J.) 1 April 1981 see page 1, line 98 - line 106 ---	1-12
A	GB,A,1 012 585 (BARNES-HIND LABORATORIES, INC.) 8 December 1965 see page 2, line 34 - line 39 see claim 1 ---	1-12
A	DATABASE WPI Section Ch, Week 8401, Derwent Publications Ltd., London, GB; Class B05, AN 84-002869 & JP,A,58 198 421 (KOSAKA R.) 18 November 1983 see abstract -----	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

22 December 1993

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB93/01873

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 9,11,12 are directed to a method of treatment of
(diagnostic method practised on) the human/animal body, the search has been
carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/GB 93/01873

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-2057263	01-04-81	US-A- 4296130	20-10-81
		AU-B- 544254	23-05-85
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		US-A- 4616039	07-10-86
		US-A- 4863748	05-09-89

GB-A-1012585		NONE	
